REMARKS

Claim 1 is amended to incorporate the subject matter of claim 46, which is now canceled. The amendment to claim 35 is supported at least by page 25, lines 23-30 in the specification.

STATUS OF CLAIMS

This application contains claims 1-46. Claims 2-4, 9, 27-29, 31-33, 36-42, and 46 have been canceled. Claims 16-26 and 34 have been withdrawn. Claims 1, 5-8, 10-15, 30, 35, and 43-45 are currently under examination and all of these claims stand rejected.

SUMMARY OF CLAIMED SUBJECT MATTER

The subject matter of the currently pending claims relates to bioscaffolding materials for treating injured or diseased body tissue. *See* specification, e.g., at pg. 3, lns. 7-18.

Claim 1

Independent claim 1 is directed to a method of producing a decellularized extracellular matrix material containing a growth factor. The body tissue of a primate or domesticated animal is conditioned (e.g., by gene transfection) *in vivo* to increase the production of a growth factor. *See* specification, e.g., at pg. 3, ln. 28 – pg. 4, ln. 26. The body tissue is harvested and decellularized to obtain an extracellular matrix material containing the growth factor. *See* specification, e.g., pg. 4, lns. 27-31. The decellularizing step involves the use of a protease inhibitor. *See* specification, e.g., at pg. 26, ln. 29 – pg. 27, ln. 14. The decellularizing step is performed without substantially altering the histoarchitecture of the body tissue. *See* specification, e.g., at pg. 25, lns. 23-30.

Claim 35

Independent claim 35 is directed to a method for producing a tissue regeneration scaffold that can be used for implantation into a patient. The body tissue of a primate or domesticated animal is conditioned (e.g., by gene transfection) *in vivo* to increase the production of a growth factor. *See* specification, e.g., at pg. 3, ln. 28 – pg. 4, ln. 26. The body tissue is harvested and decellularized to obtain an extracellular matrix material containing the growth factor. *See* specification, e.g., pg. 4, lns. 27-31. The decellularizing step involves the use of a protease

inhibitor. *See* specification, e.g., at pg. 26, ln. 29 – pg. 27, ln. 14. The decellularizing step is performed such that the extracellular matrix microstructure of the body tissue is substantially preserved. *See* specification, e.g., at pg. 25, lns. 23-30.

GROUNDS OF REJECTION TO BE REVIEWED

Whether claims 1, 5, 8, 10-12, 14, 15, 35, and 43-46, which stand rejected under 35 U.S.C. 103(a), are non-obvious over U.S. Patent No. 5,830,708 ("Naughton") in view of U.S. Patent Application Publication No. 2002/00115208 ("Mitchell"), U.S. Patent No. 7,087,089 ("Patel"), and WIPO Publication No. WO 99/55379 ("Wolff").

Whether claims 13 and 30, which stand rejected under 35 U.S.C. 103(a), are non-obvious over Naughton in view of Mitchell, Patel, Wolff, and WIPO Publication No. WO 98/39035 ("Herlyn").

Whether claims 6 and 7, which stand rejected under 35 U.S.C. 103(a), are non-obvious over Naughton in view of Mitchell, Patel, Wolff, and U.S. Patent No. 6,656,916 ("Schwarz").

ARGUMENT

A. Rejection of Claims 1, 5, 8, 10-12, 14, 15, 35, and 43-46 Under 35 U.S.C. § 103(a) Over Naughton in view of Mitchell, Patel, and Wolff.

Naughton describes methods for producing extracellular matrix material by culturing extracellular matrix-secreting human stromal cells on a biocompatible three-dimensional framework *in vitro*. *See* Abstract. After secretion of the extracellular matrix onto the framework, the stromal cells are killed, and the cells and cellular contents are removed from the framework. *See* Abstract. As conceded by the Office Action, Naughton does not teach the step of conditioning body tissue of a donor animal *in vivo*. Rather, Naughton cultures and conditions tissue *in vitro*. Thus, the Office Action combines Naughton with Mitchell for its teaching of *in vivo* culturing as an alternate to culturing tissue *in vitro*.

Mitchell describes methods for producing tissue engineered constructs by growing cells *in vitro* on a substrate and then decellularizing the construct to produce a decellularized construct consisting largely of extracellular matrix components. *See* Abstract. A substrate is seeded with cells and as the cells grow, they secrete extracellular matrix protein (such as collagen and elastin) onto the substrate. *See* col. 8, lns. 28-33. Mechanical, electrical, or chemical stimuli can be applied to the cells to stimulate the development of desired properties. *See* col. 8, lns. 39-41.

Because the method of Mitchell relies on the use of an artificial substrate for seeding of the cells, "production of the tissue engineered construct involves culturing the developing tissue *primarily* in vitro." *See* col. 8, lns. 46-48 (emphasis added). However, while indicating that the method is "*primarily* in vitro," Mitchell mentions briefly in passing that "culturing the tissue in vivo are also within the scope of the invention." *See* col. 8, lns. 46-48.

Its method being primarily applicable to *in vitro* culturing, Mitchell provides guidance on how the *in vitro* culturing should be done, including the shape and composition of the artificial substrate (col. 12, ln. 35 – col. 13, ln. 15), the different cell types that can be used to seed the substrate (col. 13, lns. 16-45), how the substrate should be seeded (col. 14, lns. 33-48), the quantity of cells needed to seed the substrate (col. I4, lns. 37-41), the type of culture media that should be used (col. 15, lns. 15-27), and the culture conditions that need to be controlled (col. 15, lns. 31-35). In contrast, Mitchell provides no specific information about how *in vivo* culturing and/or conditioning should be performed.

1. The claimed invention, as a whole, is not taught by the cited references.

The claimed method is more than simply the combination of just any conditioning process, for increasing just any biologic material in the extracellular matrix, with just any decellularizing process. In the claimed method, there is a synergistic, functional relationship between the growth factor, the extracellular matrix, and the decellularizing step using a protease inhibitor that work together to produce an extracellular matrix material having an improved ability to treat a patient's diseased or damaged body tissue.

MPEP 2141.02 instructs that a proper obviousness analysis requires a determination of "whether the claimed invention *as a whole* would have been obvious," rather than simply determining the differences between the prior art and the claims. Thus, it is improper to argue that a claim is obvious simply because each element of the claim, taken by themselves, can be found somewhere in the prior art. Applicants respectfully submit that the claimed method, as a whole, is not appreciated or suggested by the cited references.

In the claimed method, the conditioning step is for increasing the quantity of growth factors in the extracellular matrix. There is a functional relationship between these two elements of the conditioning step because the extracellular matrix can serve as a local depot for the storage of growth factors. *See, e.g.*, Taipale et al., "Growth factors in the extracellular matrix," FASEB Journal, vol. 11 (1997) (previously submitted). As such, the extracellular matrix material of the

present invention can provide a rapid release of growth factors into the local environment (e.g., into a wound) without the need for the time-consuming process of *de novo* protein synthesis. Thus, because the extracellular matrix can serve as a storage depot for growth factors, there is a special functional relationship in the claimed method between the growth factor and the extracellular matrix, which work together to produce an extracellular matrix material having an improved ability to treat a patient's diseased or damaged body tissue.

Moreover, the decellularizing step using a protease inhibitor works in conjunction with the increased growth factors present in the extracellular matrix. In general, these growth factors are attached to the extracellular matrix by protease-sensitive bonds. It is the proteolysis of these bonds that allows for the rapid release of the growth factors into the local environment. Therefore, during the decellularization step, proteases released from lysed or disrupted cells may cause the unwanted, premature release of the growth factors from the extracellular matrix. As a result, the growth factors would be lost from the extracellular matrix and the work performed in conditioning the body tissue to increase growth factor production would be negated. In the claimed method, the use of a protease inhibitor in the decellularizing step plays the important role of preserving the increased growth factors produced in the conditioning step.

Thus, the invention of claims 1 and 35 is more than just the sum of its parts. There is a special functional relationship between the growth factor, the extracellular matrix, and the decellularizing step using a protease inhibitor that work synergistically together to produce an extracellular matrix material having an improved ability to treat a patient's diseased or damaged body tissue.

2. Further evidence that the claimed invention, as a whole, is more than just the sum of its parts.

Claim 1 recites that the decellularizing step is performed without substantially altering the histoarchitecture of the body tissue; claim 35 recites that the decellularizing step is performed such that the extracellular matrix microstructure of the body tissue is substantially preserved. Thus, the method of the claimed invention preserves the body tissue's extracellular matrix structure and this allows the growth factors to be presented in their native three-dimensional organization.

As further evidence that the claimed invention, as a whole, is more than just the sum of its parts, Applicants submit that the art has come to recognize that the three-dimensional organization of the growth factors in *in vivo*-derived extracellular matrix results in superior

performance compared to extracellular matrix derived from *in vitro* culturing. Applicants refer to the report by Badylak ("Xenogeneic extracellular matrix as a scaffold for tissue reconstruction," Transplant Immunology, 2004, vol. 12:367-377), which was previously submitted. Badylak was published in 2004 (*after* the filing date of the present application) and demonstrates that the three-dimensional organization of the growth factors that results from the claimed invention provides an advantage that was not appreciated until after the date of the invention.

Badylak discusses the use of bioscaffolds derived from xenogeneic (from another species) extracellular matrix. In regards to bioscaffolds made from native tissue, Badylak reports as follows:

> The composition of these bioscaffolds includes the structural and functional proteins that are part of *native* mammalian extracellular matrix. The three-dimensional organization of these molecules *distinguishes ECM scaffolds from synthetic scaffold materials* and is associated with constructive tissue remodeling instead of scar tissue.

See Abstract (emphasis added). Badylak further states as follows:

> An important characteristic of the intact ECM that distinguishes it from other scaffolds for tissue reconstruction is its diversity of structural and functional proteins. The bioactive molecules that reside within the ECM and their unique *spatial distribution* provide a reservoir of biologic signals.
>
> . . .
>
> An advantage of utilizing the ECM in its native state as a substrate or scaffold for cell growth and differentiation is the presence of *all the attendant growth factors* (and their inhibitors) in the same relative amounts that exist in nature and perhaps more importantly, in their *native three-dimensional ultrastructure.*

See pg. 369, beginning at left col., third para. (emphasis added).

With regards to the meaning of "native," Applicants refer to the cited Mitchell reference, which defines "native tissue" as tissue that is harvested from an animal or human and that remains substantially intact and substantially retains the structure in which it is naturally found within the body of the animal or human. (Mitchell, at col. 6, lns. 61-65). Thus, according to Badylak, extracellular matrix derived from *native* tissue harvested from an animal is distinguished from synthetic scaffolding materials (such as those made using *in vitro* techniques) by the growth factors being present in their "native three-dimensional ultrastructure."

Applicants submit that there is a nexus between the particular combination of features in the claimed invention and what Badylak recognizes to be the particular characteristics of native extracellular matrix that gives it superior performance over synthetic scaffolding materials. The claimed invention uses "body tissue of a donor animal" (i.e., native tissue). The claimed invention also uses *in vivo* conditioning of the body tissue to increase the production of growth factors. The claimed invention also uses a protease inhibitor in the decellularizing step to, as explained above, protect the growth factors from premature release.

Badylak demonstrates that the result obtained by the claimed invention is more than simply the sum of its parts. There is a special functional relationship between the growth factor, the body tissue-derived extracellular matrix, and the decellularizing step using a protease inhibitor that work synergistically together in a manner that was unappreciated by the art at the time of the claimed invention.

3. Dependent Claim 44

In claim 44, "the conditioned body tissue is allowed to produce the growth factor *in vivo* for at least 2 days prior to harvesting the conditioned body tissue from the donor animal." In addition to the reasons given above, claim 44 is further non-obvious because none of the cited references discloses this duration of tissue conditioning for producing the growth factor *in vivo*.

B. Rejection of Claims 13 and 30 Under 35 U.S.C. § 103(a) Over Naughton in view of Mitchell, Patel, Wolff, and Herlyn.

Claims 13 and 30 depend from claim 1, and are non-obvious for the reasons given above, and the addition of Herlyn does not cure the above-mentioned deficiencies of Naughton, Mitchell, Patel, and Wolff.

C. Rejection of Claims 6 and 7 Under 35 U.S.C. § 103(a) Over Naughton in view of Mitchell, Patel, Wolff, and Schwarz.

Claims 6 and 7 depend from claim 1, and are non-obvious for the reasons given above, and the addition of Schwarz does not cure the above-mentioned deficiencies of Naughton, Mitchell, Patel, and Wolff.

INTERVIEW SUMMARY

Applicants thank Examiner Nguyen for the in-person interview on 21 July 2010. Applicants submit this Statement of Substance of Interview to summarize the interview in compliance with MPEP § 713.04.

Type of Interview: In-person

Names of Participants: Q. Nguyen (Examiner) and S. Yu (Applicant's representative)

Exhibits: N/A

Claims Discussed: The pending claims.

References Discussed: The cited references of record.

Principal Arguments of Applicants: The arguments already made of record.

Agreement: No agreement reached.

CONCLUSION

Applicant(s) respectfully request withdrawal of the rejections and submit that the present application is in condition for allowance. The Examiner is invited to contact Applicant(s)' representative to discuss any issue that would expedite allowance of this application.

The Commissioner is authorized to charge all required fees, fees under § 1.17, or all required extension of time fees, or to credit any overpayment to Deposit Account No. 11-0600 (Kenyon & Kenyon LLP).

Respectfully submitted,

/Steven S. Yu/

Date: 22 October 2010

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